DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

m14144n

TRANSMITTED VIA FACSIMILE

September 1, 2000

Carl-Gustaf Johansson
President and Chief Executive Officer
North American Operations
AstraZeneca
1800 Concord Pike
Wilmington, DE 19850-5437

RE: NDA 19-627
Diprivan (propofol) Injectable Emulsion
MACMIS ID #9199

WARNING LETTER

Dear Mr. Johansson:

This Warning Letter concerns AstraZeneca's promotional materials and activities for the marketing of Diprivan (propofol) injectable emulsion. The materials and activities were reviewed by the Division of Drug Marketing, Advertising, and Communications (DDMAC) as part of its routine monitoring and surveillance program. DDMAC has concluded that AstraZeneca has promoted Diprivan in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. See 21 U.S.C. §§ 331(a),(b), and 352(a),(n).

Specifically, you have misbranded Diprivan by making false or misleading representations about a competitive product. The distribution by a sponsor of promotional labeling containing false or misleading representations with respect to another drug product renders the sponsor's drug product misbranded. See 21 C.F.R. §§ 201.6(a).

Violative promotional activities undertaken by AstraZeneca include the dissemination of false or misleading promotional labeling pieces for Diprivan that state or suggest that GensiaSicor Pharmaceuticals Inc.'s (GensiaSicor) propofol injectable emulsion (approved generic product) is not safe or effective, not stable, not as cost-effective as Diprivan, or not therapeutically equivalent to Diprivan. In addition, similar statements or suggestions

have been made by representatives of AstraZeneca to healthcare professionals throughout the U.S. AstraZeneca has engaged in this promotional campaign to disparage the approved generic product, notwithstanding FDA's determination that the approved generic product is safe and effective, and that Diprivan and the approved generic product are interchangeable, that is, therapeutically equivalent. Moreover, your violative activities continue despite written notification from DDMAC objecting to similar violative conduct in an untitled letter dated March 23, 1999.

This Warning Letter is not intended to, and does not, address your promotional materials and activities that promote the use of Diprivan in a manner that is truthful, balanced, and not misleading, including materials and activities that describe the distinctions between the formulations of Diprivan and the approved generic product. Furthermore, it is not intended to, and does not, address your right to seek judicial review of FDA's decision to approve GensiaSicor's propofol injectable emulsion. Your violative promotional materials and activities described in this letter, however, go far beyond describing distinctions between the formulations of your product, Diprivan, and the approved generic product. Indeed, your violative materials and activities are suggestive of a well-orchestrated campaign designed to convince healthcare providers that your competitor's product should not be used because it is unstable and, therefore, compromises patient safety.

Background

On January 4, 1999, FDA approved an abbreviated new drug application (ANDA) for propofol injectable emulsion that was submitted by GensiaSicor. The formulation used in the approved generic product differs from that of Diprivan, in that the approved generic product contains sodium metabisulfite as a preservative agent, whereas Diprivan contains EDTA as a preservative agent.

Under the Act and FDA regulations, bioequivalent and therapeutically equivalent parenteral products, such as propofol, may differ in a variety of ways, including the preservatives, buffers, or antioxidants used in the formulation. See 21 C.F.R. 314.94(a)(9)(iii). There may also be differences in the labeling, as is the case with the approved generic product, to the extent that the inclusion or exclusion of an inactive ingredient may require modification to the product label. See 21 C.F.R. 314.94(a)(8)(iv).

FDA determined that GensiaSicor's propofol and AstraZeneca's Diprivan are therapeutically equivalent with its approval of GensiaSicor's ANDA for propofol. Therefore, the products were granted an "A" rating. This rating means that the Agency considers the products bioequivalent and therapeutically equivalent; one can be substituted for the other with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product. Until and unless the

Agency's determination is changed or reversed, any promotion suggesting that Diprivan and GensiaSicor's product are inequivalent is considered false or misleading.

On March 23, 1999, DDMAC sent an untitled letter to AstraZeneca objecting to its dissemination of promotional labeling pieces for Diprivan, including two "Dear Valued Customer" letters (dated February 8, 1999, and March 12, 1999) and glossy brochures containing selected information from papers filed in a lawsuit against FDA. In its untitled letter, DDMAC notified AstraZeneca that the dissemination of these promotional materials was in violation of the Act, and therefore misbranded Diprivan, because they contained false or misleading statements or suggestions concerning the safety, efficacy, stability, and therapeutic equivalence of the approved generic product.

Specifically, we objected to these materials because they stated or suggested that the approved generic product is not therapeutically equivalent to Diprivan, and should not be substituted for Diprivan, because the generic product contains sodium metabisulfite as a preservative, unlike Diprivan, which contains disodium edetate (EDTA)[1], and because there are stability problems associated with the generic. AstraZeneca disseminated these false or misleading promotional materials for Diprivan by mail or by its sales representatives throughout the United States.

In its March 23, 1999, untitled letter, DDMAC recommended that AstraZeneca immediately cease the dissemination of all promotional labeling and the publication of any advertisements that state, suggest, or otherwise imply that the approved generic product is not equivalent to, and substitutable for, Diprivan. We find, however, that you continue to engage in the dissemination of false or misleading promotional labeling pieces for Diprivan and other violative promotional activities, notwithstanding DDMAC's prior written notification.

False or Misleading Promotional Activities by AstraZeneca's Sales Representatives

AstraZeneca's sales representatives have continued to engage in false or misleading promotional activities with respect to Diprivan and the approved generic product. Specifically, DDMAC has received numerous accounts from healthcare professionals throughout the United States that your sales representatives are promoting Diprivan in a manner that is false or misleading in violation of the Act.

---

[1] Diprivan injectable emulsion is a single-use parenteral product which contains 0.005% disodium edetate to retard the rate of growth of microorganisms in the event of accidental extrinsic contamination. EDTA is a strong chelator of trace metals – including zinc. Although there are no reports with Diprivan injectable emulsion of decreased zinc levels or zinc deficiency-related adverse events, Diprivan injectable emulsion should not be infused for longer than 5 days without providing a drug holiday to safely replace estimated or measured urine zinc losses.

In addition, an AstraZeneca sales representative made false or misleading statements about the approved generic product to a DDMAC reviewer at an anesthesia meeting. Specifically, your sales representative made false or misleading statements at your exhibit booth during the 25th Annual Meeting of the American Society of Regional Anesthesia (ASRA) in Orlando, Florida, March 30 – April 2, 2000. For example, your representative stated that the approved generic product's emulsion is unstable and is more likely to crack because its pH is lower, and that this instability compromises patient safety. She also stated that the generic's formulation turns yellow or green if it is left out, another indication of product instability, whereas Diprivan's formulation remains white.

DDMAC has determined that in Georgia, New York, California, Minnesota, and Massachusetts, AstraZeneca's representatives have made similar statements concerning the approved generic product during promotional visits to healthcare professionals. Your sales representatives have made oral statements and representations to healthcare professionals alleging that the approved generic product's formulation is unstable and of poor integrity, whereas Diprivan's formulation is not. Your representatives have alleged that the approved generic product's formulation is subject to emulsion cracking, whereas Diprivan is not. Your representatives have alleged that the approved generic product is not as effective as Diprivan, such that use of the A-rated generic product requires higher doses than Diprivan to achieve the same effect. In addition, your representatives have alleged that the generic formulation is neither bioequivalent nor therapeutically equivalent to Diprivan. Ultimately, your representatives have implied that healthcare practitioners should not use the approved generic product because it compromises patient safety.

AstraZeneca has repeatedly made these false or misleading allegations and representations, notwithstanding the Agency's determination that the approved generic product is safe, effective, bioequivalent, and therapeutically equivalent to Diprivan.

False or Misleading Promotional Labeling Pieces Disseminated by AstraZeneca

Letter to Hospital

In a letter, dated June 4, 1999, to Rush Presbyterian/St. Luke's Medical Center in Chicago, AstraZenea stated:

> "On Wednesday, May 29, 1999 the Illinois Technical Advisory Committee voted **no** to the approval of usage of a sulfite-containing propofol in any Illinois medical institution. Based on this decision, it is deemed **illegal** to substitute the sulfite containing propofol for Diprivan from this day forward.... At this time, we ask that you immediately stop any substitution of the sulfite-containing propofol for Diprivan until further notice."

These statements are false. The Illinois Technical Advisory Committee (ITAC) is a group that provides recommendations on additions to or deletions from the Illinois Formulary to the Illinois Department of Public Health. The ITAC did meet on May 29, 1999, and one of the items on the meeting agenda was a discussion of Diprivan and the approved generic product. However, according to the chairman of the ITAC, the committee decided to delay the vote concerning the interchangeability of the two products until the next meeting of the committee, which was to take place on August 25, 1999. Therefore, the ITAC did not vote to deny approval of the approved generic product, as alleged in your letter, and the statement that the ITAC voted no concerning the interchangeability of the products is false. In fact, the ITAC discussed the two products during their next meeting (August 25, 1999) and voted to add both products to the Illinois State Formulary (with a footnote concerning the difference in preservatives).

Newsletter

A representative of AstraZeneca disseminated the spring 1999 issue of the *Anesthesia Patient Safety Foundation Newsletter* to a healthcare practitioner in Minnesota during a promotional visit in July 1999. The front page of the newsletter contains a letter to the editor that states that the approved generic product is not therapeutically equivalent to Diprivan and is not as safe or effective as Diprivan. For example, the letter states that Zeneca prepared a propofol product, using a sulfite-containing product description on file with FDA, that turned yellow and "cracked" under standard emulsion shaking stress testing. The letter also suggests that this "cracking" of the emulsion may lead to fat embolism, and that the lower pH of the approved generic product raises the possibility of "lipid droplet rain out" once the new formulation comes in contact with the pH of the blood. The letter also states that "...sulfite is not as effective as EDTA as an antimicrobial in this emulsion," and "Perhaps changing a 'preservative' is usually OK, but not to sulfite, especially if the emulsion is not stable."

To the extent that AstraZeneca disseminated the newsletter in its promotion of Diprivan, the newsletter is considered promotional labeling for Diprivan. Because this labeling contains statements and suggestions that the results Zeneca obtained with a fabricated sulfite-containing propofol product are representative of quality, safety, and efficacy issues regarding the GensiaSicor propofol formulation, it is clearly false or misleading and therefore misbrands Diprivan.

Cost Analysis

During the same promotional visit, the healthcare practitioner was also given a document entitled "Possible Cost Implications of Switching to Sulfite-Containing Propofol" by your representative. This promotional labeling piece contains misleading comparative pharmacoeconomic claims regarding a fictional hospital (Brookwood) switching to the approved generic product instead of using Diprivan. The principal assertion in your

analysis is that initial savings achieved by using the approved generic product are far exceeded by the costs resulting from adverse events in sulfite-sensitive patients receiving the approved generic product.

AstraZeneca's analysis and conclusions are misleading because they are based on erroneous information. For example, your piece assumes that 0.18% of patients in the U.S. are sulfite-sensitive. The reference you offered in support of the piece, however, reports an estimate of sulfite sensitive patients in the U.S. as less than 0.05%. Therefore, out of Brookwood's 6656 annual surgical patients, it would be expected that only 3 would have sulfite sensitivity, rather than 12, as you suggest. The cost of these events, at $3000 per event, would be $9000, rather than $36,000. Using your cost calculations, Brookwood would save $21,000 per year, not lose $6,700, by switching to the approved generic product. AstraZeneca's assertion that institutions will incur a loss if they switch from Diprivan to the approved generic product is therefore misleading.

Conclusions and Requested Actions

DDMAC is concerned that AstraZeneca is demonstrating a continuing pattern and practice of violative promotional activities. Your promotional activities alleging that the use of the approved generic product results in compromised safety and efficacy have created false or misleading impressions about the generic product. Consequently, we request that you provide a detailed response to the issues raised in this Warning Letter within 15 days of the date of this letter. This response should contain an action plan that includes a comprehensive plan to disseminate corrective messages about the issues discussed in this letter to the audiences that received these misleading messages. This corrective action plan should also include:

1. Immediately ceasing the dissemination of all promotional activities and materials for Diprivan that contain violations like those outlined in this letter.

2. Assurance to FDA that AstraZeneca is not promoting Diprivan in violation of the Act, as typified by making false or misleading representations about the generic product anywhere in the U.S. or its territories and possessions.

3. Issuing a "Dear Healthcare provider" letter to all healthcare practitioners who were, or may have been, exposed to AstraZeneca's false or misleading promotional activities to correct such false or misleading impressions and information. This proposed letter should be submitted to DDMAC for review. After agreement is reached on the content and audience, the letter should be disseminated by direct mail to all healthcare providers who may have received the violative promotion.

4. A written statement of your intent to comply with "1," "2," and "3" above.

Your written response should be directed to me. If you has any questions or comments, please contact Mark Askine, R.Ph. or me, by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. DDMAC is continuing to evaluate other aspects of your promotional campaign for Diprivan, and it may determine that additional remedial messages will be necessary to fully correct the false or misleading messages resulting from your violative conduct.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #9199 in addition to the NDA number.

Failure to respond to this letter may result in regulatory action, including seizure and/or injunction, without further notice.

Sincerely,

/S/

Thomas W. Abrams, R.Ph., MBA
Director
Division of Drug Marketing,
Advertising and Communications